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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 26, 2015
From	John Feeney, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22272/Supplement 27
Applicant	Purdue Pharma L.P.
Date of Submission	December 10, 2014
PDUFA Goal Date	June 8, 2015
Proprietary Name / Established (USAN) names	OxyContin Tablets (oxycodone HCl extended-release tablets)
Dosage forms / Strength	Extended-Release Tablets 10, 15, 20, 30, 40, 60, and 80 mg
Proposed Indication(s)	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate; (b) (4)
Recommended:	Approval; opioid-tolerant patients 11 years and older

Material Reviewed	**Review Team**
Primary Medical Officer Review	Javier Muniz, MD
Statistical Review (Efficacy Study)	Feng Li, PhD, Freda Cooner, PhD
Clinical Pharmacology Review	Srikanth Nallani, PhD, Kevin Krudys, PhD, Yun Xu, PhD
Chemistry Review	Zedong Dong, PhD, Ramesh Raghavachari, PhD
Clinical Inspection Summary	John Lee, MD, Janice Pohlman, MD, MPH, Kassa Ayalew, MD, MPH

1. Introduction

OxyContin is an extended-release (ER) oral formulation of oxycodone. It is approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Purdue has submitted the current supplement in response to the FDA's Written Request (WR) for Purdue to conduct studies with oxycodone in pediatric patients. Purdue hopes to both obtain pediatric exclusivity and gain approval for new labeling for OxyContin that would include additional information for the treatment of pediatric patients.

Oxycodone is an opioid-receptor agonist that is relatively selective for the mu-opioid receptor. In the United States, it is available as oral immediate-release (IR) and ER formulations. It is

available as both single-entity and combination products. Combination products typically contain non-narcotic pain medications such as acetaminophen. One combination product contains the opioid antagonist naloxone to deter abuse. Various generic oxycodone formulations have been approved. In addition to the solid oral dosage forms of oxycodone, oral liquid IR formulations are also available. Although parenteral formulations are in use in other countries, only oral formulations are approved in the United States.

OxyContin was first approved in 1995 under NDA 20553 as the first formulation of oxycodone that allowed dosing every 12 hours instead of every 4 to 6 hours. Subsequently, reports of abuse, overdose, and death from OxyContin began to appear. The product was frequently abused after manipulations intended to defeat the ER properties, allowing the drug to be released more rapidly. Labeling for OxyContin was strengthened to add warnings about the drug's potential for misuse and abuse and several government initiatives were undertaken in the hope of reducing harm from opioids.

In 2010, a new formulation of OxyContin was approved under NDA 22272 that was designed to deter abuse. It was designed to be more difficult to crush, break, and dissolve. In 2013, the FDA determined that the reformulated product did in fact have properties that would be expected to make the product difficult to inject and to reduce abuse via snorting. The label was updated to reflect these findings. Of note, concurrent with the submission of this pediatric supplement, (b) (4)

Also in 2010, public discussions began about initiating a class-wide Risk Evaluation and Mitigation Strategy (REMS) for all Extended-Release/Long Acting (ER/LA) opioids. The ER/LA REMS was implemented in 2012.

There is a public health need for medications to manage pain in pediatric patients. Like adults, pediatric patients are subject to the pain of both malignant and non-malignant conditions. Not infrequently, pediatric patients undergo complicated orthopedic procedures that can result in pain lasting weeks to months. In addition, there are a number of painful procedures involved in both the diagnosis and treatment of pediatric medical conditions. Over the last decade, pain in pediatric patients has received increasing attention with a focus on the development of proven analgesics.

To encourage pediatric drug development, the Food and Drug Administration Modernization Act of 1997 was signed into law and established incentives for conducting pediatric studies for drugs for which exclusivity or patent protection exists. In 2002, the Best Pharmaceuticals for Children Act (BPCA) extended the provisions of FDAMA by continuing to offer an additional six months of patent exclusivity for drugs being tested for pediatric use. Later, in 2003, the Pediatric Research Equity Act (PREA) was passed and imposed certain requirements on the sponsors of new drug applications, i.e. a proposed timeline and plan for the submission of pediatric studies. The requirements of PREA are triggered by a new indication, a new dosage form, a new route of administration, a new dosing regimen, or a new active ingredient. Because the reformulated OxyContin was approved while the older formulation was still

marketed (and is not considered a new dosage form), the requirements of PREA were not triggered by NDA 22272.

2. Background

The approved label for OxyContin, in Section 8.4 Pediatric Use, states, "Safety and effectiveness of OxyContin in pediatric patients below the age of 18 years have not been established." OxyContin is indicated in adults for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The labeled indication does not distinguish between the treatment of opioid-naïve adults and opioid-tolerant adults and dosing instructions are provided for both groups of patients.

Pediatric pharmacokinetic (PK) and dosing information for IR oxycodone is available in the literature but has not been included in labeling for approved IR oxycodone products. The usual recommended starting dose for patients over six months of age is 0.1-0.2 mg/kg every 3-4 hours in patients < 50 kg and 5-10 mg every 3-4 hours for patients ≥ 50 kg.[1] Smaller per-kilogram starting doses are recommended for patients less than six months.

BPCA allows the Agency to require studies of all relevant indications using all necessary dosage forms to meet the terms of a WR. Therefore, the WR for OxyContin outlined studies in acute pain as well as chronic pain. For the acute pain indication, an immediate release liquid formulation was ultimately used. The WR described three studies and the three studies submitted by the Sponsor to address those studies are listed below.

Study 1: OXP1005

Study 2: OXP3003

Study 3: OTR3001

Study OXP 1005 was an open-label (OL) PK and safety study of IR oxycodone for acute pain. Pediatric patients birth – 4 years were enrolled. It was a multinational study, with 9 clinical sites in Europe, Canada, and the US. A total of 60 patients were enrolled; 35 of them were enrolled at US sites. A single patient was enrolled in Canada. Study OXP 1005 was completed in 2004.

Study OXP3003 was a placebo-controlled (PC) trial intended to collect PK, safety, and efficacy data for IR oxycodone for acute pain. By protocol, about 100 patients 5-16 years were to be enrolled, but the study was stopped early for administrative reasons in 2004.

[1] Berde CB, Sethna, NF. Analgesics for the Treatment of Pain in Children. N Engl J Med 2002; 347(14): 1094-1103.

Study OTR 3001 was an OL PK and safety study of OxyContin for chronic pain. Pediatric patients 6-16 years were enrolled. It was a multinational study, with 44 clinical sites in Europe, Middle East/Central Asia, Australia, Latin America, and the US. A total of 155 patients were enrolled; 134 of them were enrolled at US sites. A single patient was enrolled in Latin America and two were enrolled in Australia.

The first WR for OxyContin was issued in 1998. In it, the Sponsor was asked to perform two cross-over studies. A second WR was later issued and the three studies described in that WR were initiated in 2003. The first two were Studies OXP1005 and OXP3003 described above. The third study was OXP3004, an OL safety study to evaluate the safety of the conversion from IR oxycodone to OxyContin in patients 6-16 years.

However, in 2004, the Sponsor decided to stop the pediatric development program for OxyContin for administrative reasons. At that time, Study 1 had completed enrollment, n=60. Study 2 had enrolled 65 patients out of a planned 100. Study 3 had (b) (4).

In 2008, the Sponsor made a decision to re-start their pediatric development program and, after additional discussion with the agency, a new third WR was issued in 2010. The final version of that WR, WR #3, Amendment #2, issued in 2011 and represents the final WR upon which the current pediatric supplement is based. That WR was attached to NDA 22272.

In WR #3, Amendment #2, Studies 1 and 2 remain essentially unchanged and it was understood that Study 1 completed in 2004 would be submitted with the hope of satisfying the WR. Likewise, Study 2 which was discontinued after 65 patients were enrolled would be submitted with the hope of satisfying the WR. Study 3, the only study of chronic pain and the only study to be conducted with OxyContin itself, took on a new design with the new WR.

Study 3, Study OTR3001, was to be an OL safety and PK study of the new abuse-deterrent (AD) formulation of OxyContin in patients 6-16 years who were opioid tolerant as defined in the protocol and had pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Study 3 was conducted between 2011 and 2014. The sponsor attempted to (b) (4). Those efforts were unsuccessful.

In the current pediatric supplement, the Sponsor has submitted the three requested pediatric studies. Additionally, data has been submitted for four additional studies. Three of those studies were small or prematurely discontinued. The fourth is an OL, continuation study, Study OTR3002, that enrolled patients who had completed four weeks of OL treatment in Study 3 of the WR, Study OTR3001.

Since the current version of the WR was issued, views about the need for pediatric studies have evolved. Based on what is known about the site of action of oxycodone and what is known about the developmental maturity of the mu-opioid receptor, efficacy now can be extrapolated from adults for most pediatric age groups. However, it is not as clear that efficacy can be extrapolated below the age of 2 years and for this reason, efficacy studies for

patients birth - 2 years are required. This approach was discussed at a workshop sponsored by the FDA and summarized in the literature.[2] Based on this new approach, for mu-opioid receptor agonists already studied in adults, sponsors are only required to study the safety and PK of that product in pediatric patients 2 years and older. Because enrollment in studies in patients less than 7 years with chronic pain is considered infeasible, studies in chronic pain below 7 years are not routinely required.

For patients less than 2 years, there are a now a number of accepted pain models appropriate to this age group, recognizing that the traditional PC clinical trial may not be suitable for this patient population due to ethical concerns and difficulty assessing pain. Alternative study designs including add-on therapy and measurement of rescue use may be feasible.

The studies outlined in WR #3, Amendment #2 differed from the current approach as follows:

1) Study OXP3003 was to include efficacy assessments in patients 5 years and older with acute pain. An efficacy study in this age group would not be required under current standards.

2) There was no study described in the WR to evaluate efficacy in patients with acute pain less than 2 years.

3. CMC/Device

The studies included in this supplement used three different formulations of oxycodone. The first was the Sponsor's own proprietary oral solution. In the past, the Sponsor marketed an unapproved oral solution but the Sponsor does not currently market an oral solution (b) (4) The second formulation was the original formulation of OxyContin; this was used in the earlier studies that required an ER formulation. The re-formulated OxyContin was the third oxycodone formulation used.

There were no CMC data submitted with the original submission of this sNDA. The CMC information in support of the IR oral solution was provided to IND 29,038 for those studies and cross-referenced in this sNDA. (b) (4)

There was one important CMC issue addressed during the review of this supplement however. The CMC Review of that issue was completed by Zedong Dong, PhD with concurrence from Ramesh Raghavachari, PhD. Dr. Dong's review discusses whether the Sponsor has (b) (4)

[2] Berde et al. Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop. Pediatrics 2012; 129(2): 354-364.

(b) (4) As discussed later in this review, Study 3 did not enroll the target population 6-12 years and the distribution of ages for those enrolled in this cohort was skewed toward the older ages. Conceivably, the lack of a lower-dose-strength OxyContin tablet could have contributed to difficulty enrolling patients at the younger end of the 6-12 year age distribution. Also, OxyContin tablets are large tablets that can present a swallowing problem for younger children and a smaller tablet size could have facilitated enrollment.

Dr. Dong describes a number of interactions with the Sponsor during the review to assess the (b) (4). Finally, on May 8, 2015, a teleconference was held between the Sponsor and the agency to clarify remaining questions. Based on the available information, Dr. Dong concludes in his review, "Based on the information provided by the applicant, it appears that Purdue Pharma has made (b) (4)

Previous attempts by the Sponsor to (b) (4).

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data were presented in the supplement and no Pharmacology/Toxicology issues arose during the review.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review was completed by Srikanth Nallani, PhD with concurrence from Kevin Krudys, PhD and Yun Xu, PhD. There are no outstanding clinical pharmacology issues and labeling recommendations have been made.

As background to the new information presented in the supplement, Dr. Nallani summarized the clinical pharmacology of OxyContin as follows:

"Pharmacokinetic properties of oxycodone following single and multiple dose administration (10 – 80 mg) of OxyContin (reformulated product approved in 2010) have been fairly well investigated in adults. Dose proportionality has been established for OxyContin 10 mg – 80 mg tablet strengths for both peak plasma concentrations (Cmax) and extent of absorption (AUC). Given the short elimination t½ of oxycodone (~5 hours), steady-state plasma concentrations of oxycodone are achieved within 24-36 hours of initiation of dosing with OxyContin. Oxycodone is extensively metabolized by multiple metabolic pathways to produce noroxycodone, oxymorphone and noroxymorphone, which are subsequently glucuronidated. Noroxycodone and noroxymorphone are the major circulating metabolites.

CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone."

In support of the application, the Sponsor performed a population PK analysis of OxyContin and IR oxycodone. Dr. Nallani's review describes the analysis that involved population PK modeling based on nonlinear mixed-effects modeling (NONMEM). From Dr. Nallani's review:

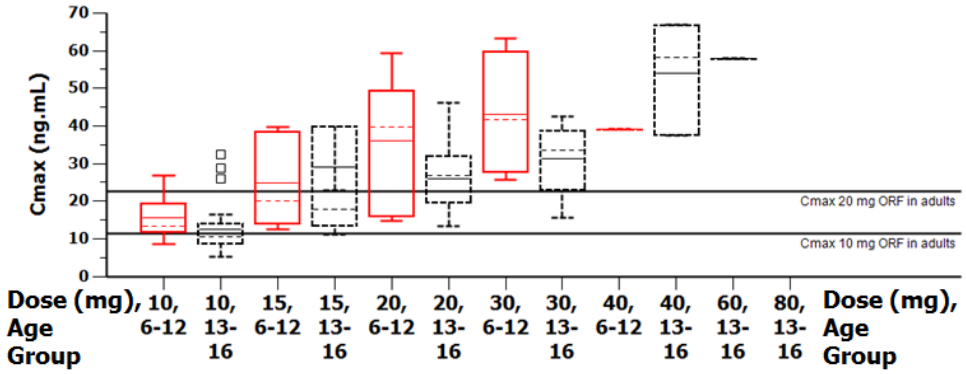
"This involved pooling of all available plasma oxycodone concentrations (intensive and sparse) from single- and multiple-dose PK studies. The pooled data represented oxycodone concentrations across a range of formulations [oral immediate release from liquid and tablet, extended release original OxyContin (OC) and reformulated OxyContin (OTR or ORF)] in pediatric patients and representative oral OxyContin data in adult subjects for the population pharmacokinetic (POPPK) dataset. A total of 5 Phase 1 and three Phase 3 clinical studies were included in the POPPK modeling of oxycodone in pediatric patients and adult subjects…The final oxycodone POP PK dataset consisted of 5567 oxycodone concentrations from 370 subjects from 8 studies…There were 255 pediatric patients (< 18 years), with weights ranging from 2.4 to 112 kg."

PK data from all three studies described in the WR were among the data included in the analysis.

The main conclusions of the analysis were as follows: "The final model identified weight as a predictor of variability in clearance (CL/F) and volume of distribution (V/F) and age as a predictor of variability in CL/F in patients less than one year of age. No other covariates investigated demonstrated any relationship in the graphical evaluation of unexplained variability in oxycodone PK."

From Study OTR3001, Dr. Nallani presents the data below.

Figure: Observed Cmax with OxyContin Dosing (10-30 mg) in Patients 6-12 Years versus Patients 13-16 Years



Consistent with the results of the Pop PK analysis, most of the differences between patients 6-12 years and 13-16 years can be explained by differences in weight. The results for patients 13-16 years are similar to what is observed in adult patients. Therefore, the Dr. Nallani recommends the following statement for labeling: "In the pediatric age group of 11 years and older systemic exposure of oxycodone is expected to be similar to adults at any given dose of OxyContin."

Dr. Nallani also notes, "…the Sponsor's pharmacokinetic model has adequately characterized the pharmacokinetics of oxycodone throughout the entire pediatric population. Therefore, this model could potentially be used to derive pediatric dosing regimens of immediate release oxycodone formulation that would match the exposure in adults at dosing regimen of FDA-approved oxycodone products." (b) (4) the Clinical Pharmacology review focused on the use of OxyContin in pediatric patients and did not develop dosing recommendations for the IR formulation in pediatric patients.

Obviously, it would be (b) (5) based on the population PK analysis described here. (b) (5) .

Dr. Lee's Clinical Inspection Summary identified an issue bearing on the integrity of the PK samples collected throughout Studies 1 and 2. Dr. Hammer at the Stanford site was an investigator in both Studies 1 and 2. The Form FDA 483 for his site noted that, "The temperature log for the freezer did not include temperature records for the first nine of the total 15 months of PK blood sample storage." Dr. Lee commented, "The inadequate freezer temperature log may indicate more than inadequate recordkeeping and may include inadequate PK blood sample handling and storage for much of the study period (nine of 15 months). A comparison of the PK data from this CI site with those from other CI sites may be helpful in evaluating the reliability of the PK data from this CI site." The comments apply to Dr. Hammer's involvement in both Studies 1 and 2. Twenty-six patients birth - 4 years were enrolled in Study 1 at his site, while an additional 26 patients 5-16 years were enrolled in Study 2 at his site.

While it remains a possibility that this deficiency only represents a recordkeeping error, a failure to record the temperature at the stated times, Dr. Nallani has attempted to reconcile the finding in his Clinical Pharmacology review as follows:

a) Document the long-term stability of the quality control (QC) solutions from the bioanalytical report;
b) Document the stability of QC solutions over the fifteen freeze/thaw cycles available from the bioavailability report;
c) He compared PK data from Study OXP3003 to another study, OXP3001. Comparable clearance values are available from both studies for 5-16 year-old patients, suggesting that the data collected in OXP3003 were valid. By extrapolation, the comparability of the PK data across these two studies for patients in the 5-16 year age group would

suggest that the PK data collected in Study OXP1005 from younger patients were also valid.

I agree that the comparable PK data across Studies OXP3003 and OXP3001 support the validity of the PK samples collected at the Stanford site for both Studies OXP3003 and OXP1005. I believe it is most likely that the lack of temperature data for the first nine months was a recordkeeping error. As such, the stability data provided by Dr. Nallani are reassuring for any short-term temperature variations that might have occurred. However, the stability of the analytes at ambient temperatures for long periods of time would be questionable. Further investigation and discussion with the Sponsor about this issue will be needed moving forward. For instance, if there were control samples stored concurrently with the patient samples in the Stanford refrigerator, the stability of those controls would provide additional evidence bearing on the validity of the patient samples. It is important to resolve this prior to any wide (b) (5) .

Dr. Nallani also addresses the Sponsor's (b) (4) . This is also addressed by the CMC review. Consistent with the CMC review, Dr. Nallani agrees that (b) (4)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The primary clinical review was performed by Javier Muniz, MD. The statistical review of the clinical efficacy study was performed by Feng Li, PhD with concurrence from his Team Leader, Freda Cooner, PhD.

The Sponsor does not propose changing the Indication and Usage section of labeling. The indication would remain "…for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." The Sponsor proposes to include in the Pediatric Use section of labeling the following statement: (b) (4) In Dosage and Administration, the Sponsor proposed the following statement: (b) (4)

As discussed earlier in this review, the current approach for mu-opioid receptor agonists is to allow extrapolation of efficacy in adults to pediatric patients 2 years and older if the PK

exposure is comparable between adult and pediatric patients. With this approach, the PK data provided in the supplement and discussed in Section 5 of this review allows for the extrapolation of efficacy of OxyContin to patients 6 years and older (6 years being the youngest age studied in Study OTR3001). Therefore, there is no need for adequate and well-controlled efficacy data for OxyContin and none has been submitted.

Using that same approach, the efficacy of an IR oral oxycodone product could be extrapolated to patients 2 years and older for the treatment of acute pain. In fact, consistent with the WR that was issued, the Sponsor submitted the results of a PC, parallel-group trial that investigated the efficacy of oxycodone 0.1 mg/kg and 0.2 mg/kg in the treatment of acute pain in patients 5 years and older. As outlined below, this study, Study OXP3003, suffered from a number of methodological problems. Among them, the study was stopped early in 2004 when the Sponsor ceased their pediatric development program, no doubt leaving the study underpowered. As described in the reviews of Dr. Muniz and Dr. Li, the efficacy results from the study are not persuasive, but, importantly, the trends observed in the study do not contradict the efficacy that would be extrapolated based on adult efficacy and comparable PK exposure in pediatric patients. As described in Dr. Nallani's review, dosing guidelines for an oxycodone IR oral solution can be developed with the information in this supplement. (b) (5), (b) (4)

Current agency policy does not allow extrapolation of efficacy in adults to pediatric patients younger than 2 years. The agency now requires that efficacy trials be conducted in patients younger than 2 years and designs for those trials have been discussed.[3] At the time of the WR, such an efficacy trial was not required for the acute pain indication. (b) (5), (b) (4)

Assessments of pain were collected throughout all three of the trials that were the subject of the WR. Other than Study OXP3003 for acute pain, no other studies were capable by design of assessing the efficacy for acute or chronic pain. Without control groups, the results of the pain assessments are difficult/impossible to interpret.

Study OXP3003

Study OXP3003 was a randomized, double-blind, PC, parallel-group study of the efficacy, safety, and pharmacokinetics (PK) of immediate-release (IR) oxycodone liquid for the treatment of acute moderate to severe pain. Pediatric patients 5-16 years were randomized to three groups: IR oxycodone oral solution 0.10 mg/kg, IR oxycodone oral solution 0.20 mg/kg, or placebo. It was a multinational study with 13 clinical sites in Europe, Canada, and the US. A total of 68 patients were randomized, sixty-one patients in the US, six in Europe, and one in

[3] Berde et al. Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop. Pediatrics 2012; 129(2): 354-364.

Canada. A single site, Dr. Hammer's site at Stanford, accounted for almost half of all patients; he enrolled 26 patients.

The original protocol for the study was finalized by Purdue Pharma in 2002. There were several subsequent protocol amendments prior to study initiation that, among other things, clarified that patients must be opioid naïve at study entry or pre-operatively (for surgical patients) and that oxygen saturation would be monitored continuously for all patients when asleep and unattended. The study was conducted from January 2003 to April 2004, when it was terminated early for administrative reasons. The clinical study report was finalized and signed in 2011.

Study OXP3003 provided PK and safety data for IR oxycodone in patients 5-16 years. It also provided supportive efficacy data for IR oxycodone for the treatment of acute pain.

The WR asked that the study be powered to show a difference in pain scores between the randomized treatment groups. In fact, pediatric patients should not experience pain unnecessarily and a study designed to show such a difference could not be conducted ethically. The intent of the WR was for the differential use of rescue medication to serve as the outcome for the trial. Similar pain scores across treatment groups, but with the greater use of rescue medication by patients in the placebo group is in fact what was observed in the study.

However, no primary outcome and no primary analysis plan were provided in the protocol and the primary objective of the protocol was stated to be characterization of the PK and safety of IR oxycodone. Therefore, both Dr. Muniz and Dr. Li have highlighted the fact that any efficacy analyses provided by the Sponsor are by nature post hoc and unadjusted for multiplicity. The protocol-stated sample size was about 100, but the study was stopped prematurely for administrative reasons in 2004 with a final n=65. If the study had been powered to show a difference in use of rescue medication, it would no doubt have been underpowered with this number of patients.

Study Design

All patients were to receive patient-controlled analgesia (PCA) or oral morphine sulfate as supplemental pain medication during the double-blind treatment period. After randomization, patients received study medication every 6 hours for 18 to 24 hours (4 to 5 doses).

The study was stratified into two age groups (5 years to <12 years and 12 years to ≤16 years). Patients were randomized to receive treatment with 0.1 mg/kg IR oxycodone, 0.2 mg/kg IR oxycodone, or placebo and they were randomization on a 3:3:2 ratio.

For efficacy, pain scores (pain right now) were obtained using the Faces Pain Scale – Revised (FPS-R) at the following timepoints: at baseline, 0.5, 1, 2, and 3 hours post-first-dose. For subsequent doses, pain scores were to be collected pre-dose and 1 hour post-dose. Pain scores were also to be obtained at the end of study. The FPS-R consists of 6 facial expressions. Each face is 25 x 35 millimeters with 13 millimeters between faces. Each patient was asked to point

to the face that reflected his or her pain. The end points are 0 = no pain and 10 = very much pain.

All doses of PCA morphine were to be recorded by total amount of morphine (mg) administered per one-hour time periods, number of doses in one-hour time periods, and route of administration. All other supplemental pain medications were also to be recorded.

For the PK evaluation, a maximum of eight blood samples (when feasible) were to be collected over the entire study period. Blood samples were to be tested for oxycodone, oxycodone metabolite, and morphine concentrations. Blood samples were to be obtained from an indwelling cannula or from a previously inserted central venous catheter or arterial catheter. Time windows for the samples were pre-designated in the protocol.

Safety was to be assessed using adverse events, clinical laboratory tests, vital signs, physical examinations, oxygen saturation, and somnolence. Oxygen saturation and somnolence were to be obtained immediately prior to each dose and one hour after each dose and, again, at the end of the study. The University of Michigan Sedation Scale (a categorical scale 0=awake to 4=unarousable to stimuli) was to be used to assess somnolence.

Primary Outcome Measure

There were two primary objectives stated in the protocol: to characterize the PK of oxycodone liquid in pediatric patients 5-16 years and to evaluate the safety.

Secondary Outcome Measure

The key secondary objective was to characterize the efficacy based on supplemental analgesic requirements and pain scores.

Inclusion Criteria

- Male and female pediatric patients from 5 to ≤16 years of age
- Anticipated to have moderate to severe pain requiring conversion to treatment with an oral opioid analgesic for 2 or more days
- Must be inpatient at the time of enrollment
- Weight must be ≥15 kg at the time of study entry
- Patients of child-bearing potential must have a negative urine pregnancy test and must be using an acceptable form of birth control
- Sufficiently alert to communicate and perform study related procedures
- Written informed consent from parent or legal guardian and child assent if appropriate
- Postoperative surgical patients receiving intravenous PCA for pain control will be eligible for inclusion

Exclusion Criteria

- American Society of Anesthesiologists Physical Status ≥4 (severe, life threatening

disease), except that patients with cancer who meet this criterion may be enrolled

- Unable to take clear liquids
- History of sleep apnea
- Cystic Fibrosis
- Malabsorption syndromes
- Sickle Cell Anemia
- Unable to take morphine
- Current oxycodone therapy (within 72 hours of study entry)
- Receiving clonidine or dexmedotomidine for sedation/analgesia
- Requiring mechanical ventilation
- Anticipated need for or currently taking NSAIDs or acetaminophen (paracetamol) other than for pyrexia
- Patients contra-indicated for the use of opioids
- Nonsurgical patients who have taken opioids within 30 days prior to study entry

Prohibited medications during the study included inhibitors of CYP3A and CYP2D6.

Primary Analysis Plan

PK

Estimates of the population mean and population variability for oxycodone PK parameters were to be derived using a nonlinear mixed effects model, i.e. a population PK approach. Exploratory analyses were to be performed to investigate the effect of age and Tanner staging of puberty. Pharmacokinetic parameters were then to be compared descriptively to those previously obtained in the adult population.

Efficacy

Supplemental pain medication usage (IV morphine equivalent) was to be summarized descriptively, 1) by treatment group, dose number and time post dose; 2) by the average supplemental pain medication usage (total usage divided by total time) during the first dose of study medication; and 3) by the overall average supplemental pain medication usage (total usage divided by total time, excluding the first dose). A statistical test (Jonckheere's test) for dose response was to be done for the average during the first dose and for the overall average. However, it was anticipated that the analysis would not show a dose response and that the confidence intervals would be too wide to conclude equivalence. The study was not powered to compare treatment groups for these parameters.

Pain scores were to be summarized descriptively also and a Jonckheere's test for dose response was also planned using the pain scores.

Safety

Safety variables were to be summarized descriptively, including somnolence, oxygen saturation, and respiratory rate.

Sample Size

By protocol, a sufficient number of patients was to be enrolled to achieve 100 PK-evaluable patients, with approximately equal numbers of patients in the 5 to <12 year old age group and

the 12 to ≤16 year old age group. Patients were to be approximately evenly distributed over the entire age range within each age stratum and across both genders. By protocol, the sponsor was allowed to monitor accrual by gender and age and to close enrollment for any particular combination of age and gender (in order to improve balance).

PK data obtained in Study OC96-0602 was used to determine the sample sizes for both Study OXP3003 and Study OXP1005.

Results

Patient Disposition and Baseline Demographics

The study was terminated early for administrative reasons in 2004. Sixty-eight patients were randomized. Three discontinued before receiving study drug. The table below Dr. Muniz's review shows the disposition for the remaining 65 patients.

Table: Patient Disposition, Study OXP3003

		Oxy Pediatric Liquid 1mg/ml		
Age Group	**Placebo (n = 19)**	**0.1 mg/kg (n = 24)**	**0.2 mg/kg (n = 22)**	**Total (N = 65)**
All Patients				
Completed, n (%)	15 (78.9)	18 (75.0)	21 (95.5)	54 (83.1)
Discontinued, n (%)	4 (21.1)	6 (25.0)	1 (4.5)	11 (16.9)
Adverse event	1[a] (5.3)	1 (4.2)	0	2 (3.1)
Subject's choice	3 (15.8)	3 (12.5)	1 (4.5)	7 (10.8)
Administrative	0	2 (8.3)	0	2 (3.1)
Age Group: 5 to <12 years	**n = 7**	**n = 10**	**n = 9**	**N = 26**
Completed, n (%)	6 (85.7)	7 (70.0)	9 (100.0)	22 (84.6)
Discontinued, n (%)	1 (14.3)	3 (30.0)	0	4 (15.4)
Adverse event	0	1 (10.0)	0	1 (3.8)
Subject's choice	1 (14.3)	1 (10.0)	0	2 (7.7)
Administrative	0	1 (10.0)	0	1 (3.8)
Age Group: 12 years to ≤ 16	**n = 12**	**n = 14**	**n = 13**	**N = 39**
Completed, n (%)	9 (75.0)	11 (78.6)	12 (92.3)	32 (82.1)
Discontinued, n (%)	3 (25.0)	3 (21.4)	1 (7.7)	7 (17.9)
Adverse event	1 (8.3)	0	0	1 (2.6)
Subject's choice	2 (16.7)	2 (14.3)	1 (7.7)	5 (12.8)
Administrative	0	1 (7.1)	0	1 (2.6)

[a] Patient experienced a pretreatment-emergent AE (vomiting) before placebo administration.

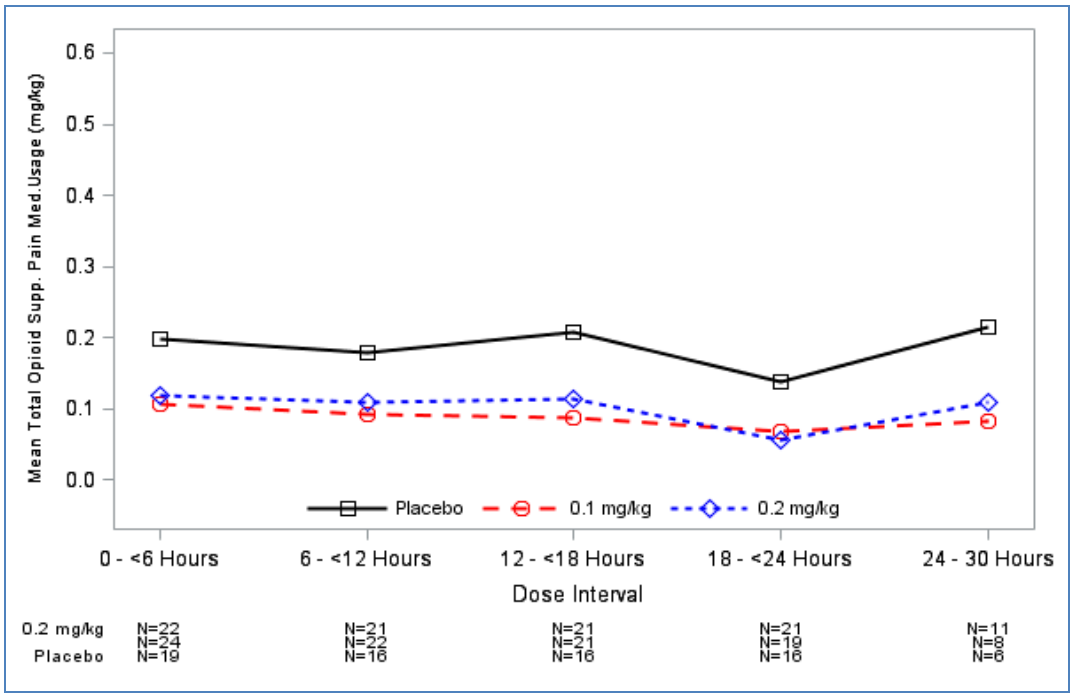
Dr. Muniz presents the baseline medical conditions for patients enrolled in the study. His review does not delineate the single medical/surgical condition that required enrollment in the present study. However, from Table 7 in Dr. Muniz's review, almost 97% of patients had baseline disorders listed that fell into the "Surgical and Medical Procedures" category, supporting post-operative or post-procedural pain as the primary reason for enrollment in the study for most patients.

Results

Despite the limitations in the analysis plan for the study, Dr. Li states, "Nevertheless, all the analyses results were numerically in favor of oxycodone in comparison to placebo."

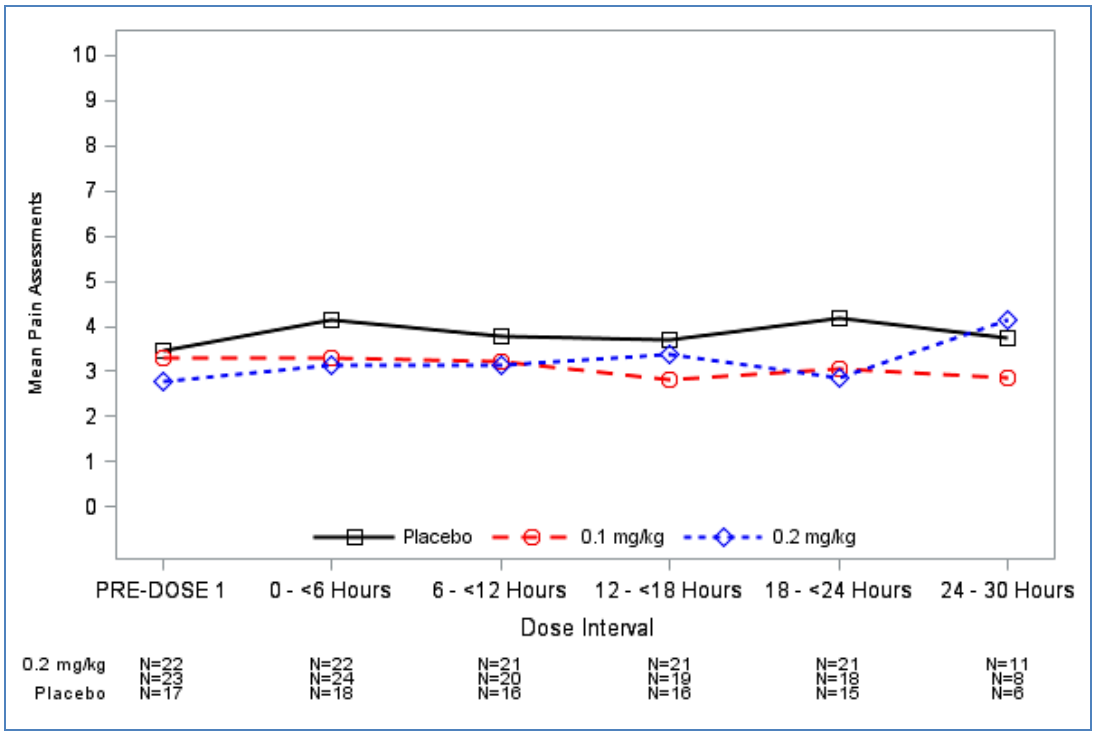
The following figures from Dr. Li's review depict both the average pain scores over time and the use of rescue medication over time. Review of the graphs suggests that the two oxycodone dose groups performed similarly in terms of pain scores and supplemental opioid usage. Therefore, dose response was not established by the study.

Figure: Total Supplemental Opioids by Dose Interval



(Source: NDA 022272 Statistical Review, Figure 2, page 12)

Figure: Pain Assessments by Dose Interval



(Source: NDA 022272 Statistical Review, Figure 1, page 12)

Subgroup Analyses by Age, Gender, and Race

The majority of patients enrolled were white, so subgroup analyses for race were not conducted. Differences between the treatment groups for supplemental opioid usage were more apparent for the older age group than the younger age group. Pain curves may separate by treatment group more for males at some time point. The supplemental opioid usage curves appear similar by gender.

Efficacy Conclusions

As described in the reviews of Dr. Muniz and Dr. Li, the efficacy results from the study are not persuasive, but, importantly, the trends observed in the study do not contradict the efficacy that would be extrapolated based on adult efficacy and comparable PK exposure in pediatric patients 5-16 years. There was no persuasive evidence for dose-response in the study.

8. Safety

The primary review of the safety data was performed by Javier Muniz, MD.

The safety database submitted in the NDA contains safety data from seven clinical studies, the three studies that are the subject of the WR and four additional studies described in the

previous section. One of the seven submitted studies, Study OTR3002, was an OL extension study of Study OTR3001 and enrolled only patients that had completed four weeks of OL treatment with OxyContin in Study OTR3001. The other six studies are pooled by the Sponsor and referred to as Group B in the submission. All the studies differed in many ways. Differences in the studies included different indications (acute versus chronic pain), different treatment durations, different age groups, and different study designs.

The total exposure in the pooled study data was 314 unique subjects exposed to at least one dose of OxyContin. Of the 314 patients, 261 were included in the three studies described in the WR.

Because of the differences across studies, Dr. Muniz discussed most safety data by individual study. However, deaths and serious adverse events (AEs) were pooled for discussion. Study OTR3002, the OL continuation study is discussed separately.

Deaths

There were four deaths across all studies. Dr. Muniz provides narratives for all four. None of them can be reasonably attributed to study drug. All four patients had underlying malignant neoplasms.

Nonfatal Serious Adverse Events (SAEs)

Thirty-five patients in five of the seven studies experienced non-fatal SAEs. There were no SAEs in two studies, Study OC96-0602 and Study OXP3004.

Dr. Muniz has characterized 32 of the SAEs as unrelated to study drug or unlikely related to study drug. The SAEs that he deemed unrelated to study drug include a number of cases of neutropenic fever, surgical complications, and sickle-cell-related events. He believes one SAE is possibly related to study drug and two SAEs are probably/likely related to study drug.

Subject 0006003 in Study OTR3001 experienced an SAE of diplopia, intermittent vomiting, vertigo, disequilibrium, dizziness, headache, and lethargy. This was a 16-year-old female with a history of acoustic neuroma removal. After three days on OxyContin, she developed dizziness, nausea, emesis, and blurry vision resulting in hospitalization. She also complained of no bowel movements for nine days. She had an ataxic gait on admission. Study drug was discontinued and the symptoms reportedly resolved. The patient was discharged from the hospital after one day. Dr. Muniz believes the events were likely related to study drug.

Subject 0027001 in Study OTR3002 (OL-extension study of OTR3001) experienced an SAE of constipation resulting in hospitalization. This was a 10-year-old male with a history of multiple medical problems including nephroblastoma, osteomyelitis, and MRSA infection. He was treated for constipation after five months of treatment with OxyContin. Two months later, and two weeks after stopping OxyContin, the patient was admitted with a history of no bowel movement for two weeks. The patient was treated and was discharged the next day. Dr. Muniz believes the event was probably related to OxyContin.

Subject 0038008 in Study OXP1005 experienced an SAE of obstructive apnea. This was a 13-day-old neonate with a history of patent ductus, repair of esophageal atresia and trachea-esophageal fistula, and obstructive apnea prior to treatment with oxycodone. After the initial treatment with 0.05 mg/kg, he developed the apnea. The event was attributed to the failure of successfully suctioning excessive and thick nasal secretions. The event was treated with suctioning, re-intubation, and bag ventilation. Oxycodone was stopped and the patient was discontinued from the study. Dr. Muniz believes the event was possibly related to study drug.

In addition to the above three patients, I believe the following SAE could possibly be related to study drug.

Subject 0075020 in Study OTR3001 experience an SAE of pancreatitis. This was a 15-year-old female who had a history of pancreatitis 11 years earlier. She had recent spinal fusion surgery for scoliosis. After five days of OxyContin, she complained of mild abdominal pain and constipation. The evaluation of the abdominal pain revealed an elevated amylase of 193 U/L (normal range: 13-60 U/L). Three days later, the amylase had increased to 261 U/L and the patient was admitted to the hospital. The patient was discharged after one day and the SAE was considered resolved by the investigator who attributed the pancreatitis to the patient's previous history of pancreatitis. While Dr. Muniz considers the event unlikely related to study drug, I would consider it possibly related to study drug.

INDIVIDUAL STUDIES

The three clinical studies that were the subject of the WR included 261 patients. A fourth study, Study OTR3002, was an OL continuation study of one the WR studies; 23 patients from Study OTR3001 continued with treatment in Study OTR3002. Across three additional studies, OTR1020, OC96-0602, and OXP3004, there were an additional 53 patients treated. In each study, patients were treated with OxyContin, IR oxycodone, or both. Where OxyContin was used, it may have been the original formulation or the currently-available abuse-deterrent formulation.

1. Study OXP1005, Open-Label Safety Data with Three Dosing Cohorts Birth – Four Years, IR Oxycodone

Study OXP 1005 was an OL PK and safety study. Pediatric patients birth - 4 years were enrolled. It was a multinational study, with 9 clinical sites in Europe, Canada, and the US. A total of 60 patients were enrolled; 35 of them were enrolled at US sites. A single patient was enrolled in Canada. The study was conducted from January 2003 to April 2004, when it was terminated early for administrative reasons (although enrollment was near complete). The clinical study report was finalized and signed in 2011.

After the protocol was finalized, there were several subsequent protocol amendments prior to study initiation that, among other things, 1) clarified that patients must be opioid naïve at study entry or pre-operatively (for surgical patients); and 2) changed the planned age strata

From:

> Patients will be stratified into three age groups (birth to 30 days, 31 days to <1 year, and 1 year to 4 years), and will be approximately evenly distributed over the entire age range in each age stratum and across both genders.

To:

> Patients will be stratified into three age groups (birth to 30 days, 31 days to ≤ 6 months, and 7 months to ≤ 4 years), and will be approximately evenly distributed over the entire age range in each age stratum and across both genders.

Dr. Muniz presents the baseline medical conditions for patients enrolled in the study. His review does not delineate the single medical/surgical condition that required enrollment in the present study. However, from Table 25 in Dr. Muniz's review, almost 97% of patients had baseline disorders listed that fell into the "Surgical and Medical Procedures" category, supporting post-operative or post-procedural pain as the primary reason for enrollment in the study for most patients.

Discontinuations due to AEs

Three out of the 60 patients (5%) enrolled in the study discontinued for AEs. The AEs that led to discontinuation were apneic episode, vomiting, and somnolence. Patient 0038008 experienced the apneic episode and is discussed under SAEs. The patient with vomiting was a 10-day-old neonate who had a congenital intestinal malformation and had experienced vomiting even prior to the use of study drug at a dose of 0.05 mg/kg every six hours. The patient with somnolence was a 2-month-old boy who was receiving 0.2 mg/kg oxycodone every six hours.

There was not a preponderance of AE discontinuations in any of the three dose groups, 0.05 mg/kg, 0.1 mg/kg, or 0.2 mg/kg. The AE discontinuations also did not cluster in any of the three age cohorts, birth - 30 days, 31 days - 6 months, or 7 months - 4 years. Note that all patients in the birth – 30 days cohort were treated with 0.05 mg/kg.

There were two patients who discontinued for "subject's choice" and five patients who discontinued for administrative reasons. None of the reasons for the administrative discontinuations were concerning. The underlying events leading to the "subject's choice" discontinuations are not known and the case report forms for these patients are not included in the submission.

Common AEs

The table below from Dr. Muniz's review shows the all AEs for the birth – 30 days cohort. None of the common AEs observed were considered severe by the investigator. Dr. Muniz notes that half of these patients were less than a week old.

Table: Adverse Events for the Birth – 30 Days Cohort, Study OXP1005

MedDRA Preferred Term	CI's Assessment of Severity			Total n (%)
	Mild n (%)	Moderate n (%)	Severe n (%)	
Haemoglobin decreased	2 (22.2%)	0	0	2 (22.2%)
Atelectasis neonatal	1 (11.1%)	0	0	1 (11.1%)
Blood pressure diastolic decreased	1 (11.1%)	0	0	1 (11.1%)
Blood pressure systolic increased	1 (11.1%)	0	0	1 (11.1%)
Hyperbilirubinaemia neonatal	0	1 (11.1%)	0	1 (11.1%)
Infantile apnoeic attack	0	1 (11.1%)	0	1 (11.1%)
Respiratory rate decreased	1 (11.1%)	0	0	1 (11.1%)
Vomiting neonatal	0	1 (11.1%)	0	1 (11.1%)
Total (% of TEAEs for age group)	6 (66.7%)	3 (33.3%)	0	9 (100%)

Reference: Reviewer-constructed with JMP v11.)
Individual patients can have more than one TEAE.
Percentages are based on number of TEAEs.
CI = Clinical investigator

Dr. Muniz summarizes the AEs for the other two age cohorts as follows:

"In the 31 days to ≤6 month-old cohort there were no severe TEAEs in 24 patients. In total, there were 13 TEAEs reported by 8 (33.3%) of the 24 patients. Only two Preferred Terms surpassed the threshold of occurring more than once: "vomiting" with 4 events (all considered "mild" in severity) but all reported by 1 (4.2%) patient and "hypertension" with 2 events (all considered "mild" in severity) in 2 (8.3%) patients. Just like in the youngest cohort of this study, the small number of patients in this age cohort limits the generalization of this conclusion. In this age cohort, patients were distributed evenly on each of the three dose regimens (0.05mg/kg, 0.1mg/kg, and 0.2mg/kg). The age distribution within this group was distributed fairly evenly throughout the age spectrum.

In the 7 months to <4 years-old age group there were no serious TEAEs. In total, there were 43 TEAEs reported by 18 (75%) of the 24 patients. The subjects in this age range were distributed evenly on each of the three dose regimens. The age distribution within this group was distributed fairly evenly throughout the age spectrum."

To look across all patients enrolled in Study OXP1005, including all age cohorts, Dr. Muniz's review includes the following table.

Table: Adverse Events for All Patients, Study OXP1005

System Organ Class Preferred Term	Oxy Pediatric Liquid 1mg/mL 0.05 mg/kg (N=26) n (%)	0.1mg/kg (N=17) n (%)	0.2mg/kg (N=17) n (%)	Total (N=60) n (%)
Any Adverse Event	**13 (50)**	**9 (53)**	**8 (47)**	**30 (50)**
Cardiac disorders	**1 (4)**	**1 (6)**	**1 (6)**	**3 (5)**
Tachycardia	1 (4)	1 (6)	1 (6)	3 (5)
Eye disorders	**0**	**0**	**1 (6)**	**1 (2)**
Eye swelling	0	0	1 (6)	1 (2)
Gastrointestinal disorders	**3 (12)**	**0**	**4 (24)**	**7 (12)**
Abdominal pain	0	0	1 (6)	1 (2)
Constipation	0	0	1 (6)	1 (2)
Nausea	0	0	1 (6)	1 (2)
Vomiting	2 (8)	0	3 (18)	5 (8)
General disorders and administration site conditions	**1 (4)**	**2 (12)**	**2 (12)**	**5 (8)**
Pyrexia	1 (4)	2 (12)	2 (12)	5 (8)
Injury, poisoning and procedural complications	**0**	**1 (6)**	**0**	**1 (2)**
Postoperative fever	0	1 (6)	0	1 (2)
Investigations	**4 (15)**	**2 (12)**	**0**	**6 (10)**
Haemoglobin decreased	2 (8)	2 (12)	0	4 (7)
Platelet count decreased	0	1 (6)	0	1 (2)
Metabolism and nutrition disorders	**0**	**1 (6)**	**1 (6)**	**2 (3)**
Decreased appetite	0	0	1 (6)	1 (2)
Hypokalaemia	0	1 (6)	0	1 (2)
Nervous system disorders	**0**	**0**	**1 (6)**	**1 (2)**
Sedation	0	0	1 (6)	1 (2)
Renal and urinary disorders	**0**	**0**	**1 (6)**	**1 (2)**
Urinary retention	0	0	1 (6)	1 (2)
Respiratory, thoracic and mediastinal disorders	**2 (8)**	**1 (6)**	**1 (6)**	**4 (7)**
Atelectasis	0	1 (6)	0	1 (2)
Pulmonary oedema	0	0	1 (6)	1 (2)
Skin and subcutaneous tissue disorders	**1 (4)**	**1 (6)**	**0**	**2 (3)**
Pruritus	0	1 (6)	0	1 (2)
Vascular disorders	**2 (8)**	**1 (6)**	**2 (12)**	**5 (8)**
Hypertension	2 (8)	0	1 (6)	3 (5)
Hypotension	0	1 (6)	1 (6)	2 (3)

(Source: OPX1005's report, Table 15, page 67)
Percentages are based on N.
Multiple occurrences of the same adverse event in 1 individual are counted only once.

Laboratory Findings

In Study OXP1005, an examination of mean changes from baseline for both hematologic and select chemistry parameters was remarkable only for a mean change from baseline in absolute neutrophil count. The overall mean change was -2405/microliter and the change was similar

across all three dose groups (0.05 mg/kg, 0.1mg/kg, and 0.2 mg/kg). The significance of this is unknown.

One patient in the 0.05 mg/kg group had an increase in AST from 84 U/L at baseline to 659 U/L at end of study. The values returned to normal after the study.

Vital Signs

No significant changes from baseline were noted in blood pressure, pulse, or respiratory rate.

Oxygen saturation was measured for approximately 36 hours for all patients. Dr. Muniz reviewed the results and makes it clear that on average the 0.2 mg/kg dose caused a significant reduction in oxygen saturation compared to the other two dose groups and that more patients in the 0.2 mg/kg dose group had saturations less than 90% than in the other two dose groups. What is not totally clear from his review is that the group of patients 1 month - 6 months contributed prominently to the effect seen with the 0.2 mg/kg dose on oxygen saturation. The effect was not seen on average in the patient cohort 7 months – 4 years. Note that the patients birth to 1 month were all dosed with 0.05 mg/kg. The data by age cohort is presented in Table 14.3.6.1 from the study report (the source table for Table 23 in the main body of the study report). The table below summarizes the results for the 1 month – 6 months cohort.

Table: Hemoglobin Oxygen Saturation (%) Data, Patients Ages 1-Month to 6-Months

	0.05 mg/kg n=7	0.1 mg/kg n=9	0.2 mg/kg n=8
Minimum Overall			
Mean (SD)	92.0 (4.08)	94.2 (7.43)	81.3 (11.25)
Median	94.0	96.0	76.0
Min, Max	84,95	75,99	70,97

(Source: Study OTR1005 Clinical Study Report, Table 14.3.6.1)

The Sponsor's conclusion in the study report states, "Oxygen saturation values were lower in the 0.2 mg/kg group than in the other dose groups but this difference was not clinically significant. The low values for 0.2 mg/kg group were driven by the fact that patients receiving this dose in the 31 days to 6 months group had low SpO2 at all dosing intervals (mean between 84% and 87%)."

The table below lists the pre-dose oxygen saturation values for patients 1-6 months by dosing group.

Table: Pre-Dose Oxygen Saturation Values, Patients Ages 1-Month to 6-Months

SUBJID	Oxy Pediatric Liquid Dose	Age	SPO_2 Baseline	SPO_2 Worst	SPO_2 End of Study
34004	0.05 mg/kg	3 months	91	84	91
34007		3 months	99	95	95
37001		2 months	95	95	98
37005		6 months	95	94	96
38003		4 months	95	93	97
47001		6 months	97	94	96
47006		3 months	95	89	97
34014	0.10 mg/kg	2 months	100	96	98
34015		6 months	100	99	100
34016		5 months	85	75	81
34017		3 months	100	98	100
34018		5 months	99	97	100
34019		6 months	100	95	96
37008		2 months	97	95	96
47011		5 months	97	94	99
47012		6 months	100	99	99
34020	0.20 mg/kg	5 months	78	74	81
34021		4 months	88	78	80
34022		3 months	80	72	86
34023		2 months	97	97	100
34024		4 months	99	96	100
34025		4 months	89	73	86
34026		4 months	78	74	83
47013		4 months	94	90	97

Reference: Constructed by Primary Clinical Reviewer (Dr. Muniz) with JMP v11

Patients with lower pre-dose oxygen saturation values cluster in the 0.2 mg/kg dosing group. This may reflect the fact that these are not randomized groups and the numbers of patients in each group are small. There may also have been unknown biases leading to patient assignment to certain dose groups.

There was not an operational definition of a lowest-allowed oxygen saturation for inclusion in the trial. Note however that, by protocol, patients with impaired respiratory reserve were to be excluded from enrollment. By that definition, it appears that at least three patients in the 0.2 mg/kg group may not have met inclusion/exclusion criteria.

These results deserve further exploration. An information request was sent to the Sponsor on May 26, 2015, requesting more information about the patients with low oxygen saturations at baseline. The Sponsor was asked to address the inclusion of these patients with low oxygen saturations into the trial given the inclusion/exclusion criteria regarding respiratory status.

**2. Study OXP3003, Randomized, Placebo-Controlled Trial
Six – Sixteen Years, IR Oxycodone**

See Section 7 Clinical Efficacy for an outline of the study design for Study OXP3003.

Discontinuations due to AEs

Only two patients enrolled in the study discontinued for AEs, one in the placebo group and one in the 0.1 mg/kg group. The latter patient, Patient 36002, experienced the SAE of cholelithiasis after a cholecystectomy and is discussed under SAEs. The SAE was unrelated to study drug.

Two additional patients on active drug had dose reduction or treatment interruption for AEs. An 11-year-old female on 0.1 mg/kg experienced nausea and pruritus and had a dose reduction. The dose was reduced again for continued pruritus. A 14-year-old female in the 0.2 mg/kg group had treatment interrupted because of vomiting.

There were seven patients who discontinued for "subject's choice" and two patients who discontinued for administrative reasons. These discontinuations are equally distributed between the placebo and active-drug groups. The underlying events leading to the administrative discontinuations were listed in the case report forms, but the reasons underlying discontinuations for "subject's choice" were not. The two administrative reasons given were an inability to obtain PK samples and the need for sedation for an unanticipated procedure. Of the seven "subject's choice" cases, a case report form was submitted for only one (Patient 50004) and it lists an event of hypoxia earlier in the same day that the patient discontinued. Unfortunately, the case report form does not fully clarify what transpired during the course of that day.

Common AEs

The table below from Dr. Muniz's review summarizes the common AEs across the three treatment groups. Pyrexia appears to be dose-related. Note that concomitant opioids were used as rescue medication in the trial. Therefore, the incidence of AEs across the treatment groups reflects the use of oxycodone plus any rescue medication used. The Sponsor also presented the AEs divided into two age cohorts, 6-12 years and 12-16 years. The AE profiles for the two age cohorts were comparable.

Table: Adverse Events Occurring in at Least Two Patients, Study OXP3003

MedDRA Preferred Term	Oxy Pediatric Liquid 0.10 mg/kg N = 24 n (%)	Oxy Pediatric Liquid 0.20 mg/kg N = 22 n (%)	Placebo N = 19 n (%)	Total N = 65 n (%)
Pyrexia	3 (12.5%)	8 (36.4%)	3 (15.8%)	14 (21.5%)
Pruritus	4 (16.7%)	4 (18.2%)	2 (10.5%)	10 (15.4%)
Vomiting	1 (4.2%)	3 (13.6%)	4 (21.1%)	8 (12.3%)
Nausea	1 (4.2%)	1 (4.5%)	2 (10.5%)	4 (6.2%)
Procedural nausea	2 (8.3%)	0	2 (10.5%)	4 (6.2%)
Headache	1 (4.2%)	2 (9.1%)	1 (5.3%)	4 (6.2%)
Constipation	0	2 (9.1%)	0	2 (3.1%)
Pleural effusion	1 (4.2%)	1 (4.5%)	0	2 (3.1%)
Blood pressure increased	0	1 (4.5%)	1 (5.3%)	2 (3.1%)
Hypertension	1 (4.2%)	1 (4.5%)	0	2 (3.1%)

(Source: Reviewer-constructed with JReview)
*More than one TEAE can be reported by one patient.

Laboratory Findings

In Study OXP3003, Dr. Muniz found no worrisome trends in hematologic parameters based on an examination of both mean changes from baseline and individual patient shifts from normal to abnormal. I do note that his Table 46 identifies five patients (one in the 0.1 mg/kg group and four in the 0.2 mg/kg group) with decreases in hemoglobin of about 20 g/L or more, while there is only one such patient in the placebo group. The mean change from baseline in hemoglobin is similar across the three treatment groups. Given the small numbers of patients in each treatment group, the concomitant medical problems of the patients, along with our prior knowledge of the adverse event profile of oxycodone, it is unlikely that these observations of hemoglobin changes can be attributed to oxycodone.

An examination of mean changes from baseline for chemistry values revealed a mean increase in SGPT for both oxycodone groups and a small decrease for the placebo group. The mean increase was 31 U/L for the 0.1 mg/kg group and 10 U/L for the 0.2 mg/kg group, while the decrease was -14 U/L for the placebo group. At the same time, the shift table presented by Dr. Muniz shows an SGPT shift from normal to high for one placebo patients and one 0.2 mg/kg patient. The shift table shows an SGOT shift from normal to high for no placebo patients, two 0.1 mg/kg patients, and two 0.2 mg/kg patients. There were no worrisome trends for bilirubin values. One patient in the 0.1 mg/kg group had an increase in SGPT from 172 to 719, while one patient in the 0.1 mg/kg group had an increase in SGOT from 269 to 577.

Vital Signs

Summary data for blood pressure, temperature, respiratory rate, and oxygen saturation showed no differences between placebo and the active-treatment groups.

3. Study OTR3001, Open-Label Safety Data Six – Sixteen Years, OxyContin

Study OTR 3001 was an open-label PK and safety study. Pediatric patients 6-16 years were enrolled. It was a multinational study, with 44 clinical sites in Europe, Middle East/Central Asia, Australia, Latin America, and the US. A total of 155 patients were enrolled; 134 of them were enrolled at US sites. A single patient was enrolled in Latin America and two were enrolled in Australia.

All patients were expected to require ongoing around-the-clock opioid treatment equivalent to at least 20 mg daily dose of oxycodone for at least 2 weeks for management of moderate to severe malignant or nonmalignant pain.

Patients must have been opioid tolerant defined by the protocol as "having been treated with opioids for at least the 5 consecutive days prior to dosing and with at least 20 mg of oxycodone daily and no more than 240 mg daily during at least the last 48 hours before the start of study drug dosing". Patients could have been outpatients or inpatients at the time of enrollment. Inpatients were to continue in the study upon hospital discharge.

Eligible patients were to immediately begin treatment with OxyContin tablets with the exception of postoperative patients, who could not be dosed with the study drug until at least 5 days post-surgery. Patients were to receive a total daily dose of OxyContin tablets administered in divided doses every 12 hours for a minimum of 2 weeks and up to 4 weeks. Upward and downward titration as well as asymmetric doseing was permitted, as long as the study drug was administered twice daily.

The investigators used the following sponsor-provided table to convert other opioid medications to oral OxyContin.

Table: Multiplication Factors used in Converting the Daily Dose of Prior Opioids to the Daily Dose of OxyContin

	Oral Prior Opioid	Parenteral Prior Opioid
Oxycodone	1	--
Codeine	0.15	--
Fentanyl	--	0
Hydrocodone	0.9	--
Hydromorphone	4	20
Levorphanol	7.5	15
Meperidine	0.1	0.4
Morphine	0.5	3
Tramadol	0.17	0.2

Almost all conversions in the trial were from oxycodone, morphine, hydromorphone, and/or hydrocodone.

The case report form used in this study did not require the investigator to designate the one medical/surgical condition that required enrollment in the present study. From Table 7 in Dr. Muniz's review, almost 97% of patients had baseline disorders listed that fell into the "Surgical and Medical Procedures" category, supporting post-operative or post-procedural pain as the reason for enrollment in the study for most patients. An IR was sent to the Sponsor on May 20, 2015 asking the Sponsor to provide the primary condition for which treatment with OxyContin was required.

Discontinuations due to AEs

Ten out of the 155 patients (6.4%) enrolled in the study discontinued for AEs. Four of these patients have been previously described, two deaths and two cases with SAEs. The two deaths and one of the SAE cases were considered unrelated to study drug. The second SAE case was Patient 0006003 who experienced diplopia, intermittent vomiting, vertigo, disequilibrium, dizziness, headache, and lethargy. She had an ataxic gait on admission to the hospital. The SAE was reported to have resolved with study drug discontinuation.

Dr. Muniz describes the six other AE discontinuation cases in his review. All seem related to the study drug. The AEs include: dizziness, headache, and worsened pruritus; moderate euphoria and mild urinary retention; abnormal dreams and irritability; pruritus and pruritic rash; hyperhidrosis; and urticaria.

For the seven AE discontinuations related to study drug, the time of onset of the AE ranged from a single dose (urticaria) to 12 days (hyperhidrosis). The case of hyperhidrosis resolved within two days. The AE of urticaria was listed as ongoing.

There were seven patients who discontinued for "subject's choice" and ten patients who discontinued for administrative reasons. By protocol, patients who required continued use of a daily, around-the-clock opioid for less than two weeks were classified as discontinuations and almost all the administrative discontinuations within the first two weeks were for this reason. One of the administrative discontinuations (Patient 6001) appears to have resulted when study drug was mistakenly stopped by the patient's orthopedic surgeon; the case report form for that patient is not entirely clear. Several of the four "subject's choice" discontinuations within the first two weeks were also for the same reason. Five patients discontinued for lack of therapeutic effect, one in the first two weeks and four in the second two weeks.

Common AEs

The Sponsor's table below (included in Dr. Muniz's review) summarizes the common AEs. The common AEs are consistent with AEs expected for an opioid and include nausea, vomiting, dizziness, constipation, and pruritus. Dr. Muniz compared the AE profiles for the 6-12 year cohort and the 12-16 year cohort and found them to be similar.

Table: Incidence of Adverse Events Reported in > 5% of Patients in Any Age Group

System Organ Class Preferred Term	Age Group		Total (N=155) n (%)
	6 to <12 Years (N=27) n (%)	≥12 to ≥16 Years (N=128) n (%)	
Any TEAEs	**19 (70.4)**	**89 (69.5)**	**108 (69.7)**
Gastrointestinal disorders	**12 (44.4)**	**51 (39.8)**	**63 (40.6)**
Vomiting	6 (22.2)	28 (21.9)	34 (21.9)
Nausea	3 (11.1)	20 (15.6)	23 (14.8)
Constipation	4 (14.8)	12 (9.4)	16 (10.3)
Diarrhoea	3 (11.1)	5 (3.9)	8 (5.2)
General disorders and administration site conditions	**9 (33.3)**	**28 (21.9)**	**37 (23.9)**
Pyrexia	6 (22.2)	12 (9.4)	18 (11.6)
Nervous system disorders	**3 (11.1)**	**36 (28.1)**	**39 (25.2)**
Headache	3 (11.1)	19 (14.8)	22 (14.2)
Dizziness	0	12 (9.4)	12 (7.7)
Skin and subcutaneous tissue disorders	**4 (14.8)**	**22 (17.2)**	**26 (16.8)**
Pruritus	3 (11.1)	7 (5.5)	10 (6.5)

(Source: OTR3001's study report, Table 25, page 107)
Note: Patients who experienced 2 or more adverse events within the same SOC or preferred term were counted only once.
TEAEs that occurred in >5% of patients for each preferred term in any age group are presented.
Percentages are based on N.

Laboratory Findings

In Study OTR3001, an examination of mean changes from baseline for both hematologic and select chemistry parameters did not reveal any significant trends.

It was not surprising that there were more individual outliers for laboratory abnormalities in Study OTR3001 than in the other studies in the supplement because the study was the largest of the studies in the supplement and it included a longer observation period than other studies. As in other studies, the serious concomitant medical conditions of the enrolled patients also contributed to these abnormalities. There are 24 patients with outlier values for laboratory measures discussed by Dr. Muniz in his review. Low hemoglobin values account for more than half of the 24 abnormalities and all are explained by the patients' underlying conditions (all were low at baseline). The other outlier values included two cases of elevated SGPT (414 U/L and 315 U/L). There were three cases of low platelet count with or without neutropenia, three cases of low lymphocyte count, two cases of elevated blood sugar, and one case of a low phosphorous level.

Vital Signs

In Study OTR3001, vital signs were measured during the time interval after conversion to OxyContin. Dr. Muniz reports that there were no clinically significant changes from baseline in blood pressure or pulse. He also states "…there were no patients with treatment-emergent clinically significant respiratory depression (defined as respiratory rate of ≤10 breaths per minute for patients aged over 12 years; ≤12 breaths per minute for patients aged 6 to < 12 years)."

From Dr. Muniz's review, "There was 1 patient in the 6 to less than 12 years group and 1 patient in the 12 to 16 years group with treatment-emergent clinically significant hemoglobin-oxygen desaturations (defined as $SpO_2 \leq 90\%$), each of them with one episode, and each episode occurring 3 or more hours after either the first dose or uptitration. One of them was a 15 y/o female had a minimum SpO_2 of 88% 32 hours post-dose on day 5 of the study. She died on day 19 of hypoxia from her underlying neuroblastoma... The other one was an 11 y/o female with a minimum SpO_2 of 79% 3 hours post-dose 1 on day 1 of the study. Neither of these events resulted in a reduction of the dose or discontinuation of the study drug. There were 4 patients in the total population (2 in each age group) that experienced the TEAE of oxygen saturation decreased."

4. Study OTR1020, Open-Label Safety Data, n=30
Six – Sixteen Years, OxyContin

This was an open-label study to characterize the PK and safety of single-dose and multiple-dose reformulated OxyContin (ORF) tablets in pediatric inpatients aged 6 to 16 years. Thirty patients 6-16 years were enrolled in the study. (Informed consent was obtained for an additional 12 patients, but these patients did not pass screening.) There were 25 patients 12-16 years and 5 patients 6-12 years. The study was conducted between 2010 and 2011.

Patients were postoperative and nonsurgical patients who were expected to require oral opioid treatment for at least 12 hours. Patients were required to be inpatient for the entire treatment period. By protocol amendment, postsurgical patients were required to not be dosed until at least 96 hours after surgery and all patients were required to be treated with an opioid for at least 96 hours prior to the first dose of study drug.

Study treatment lasted from 12 hours (single dose) to 72 hours (5 doses). In the study, 18 patients received only a single dose of study drug, while 12 patients received multiple doses.

One SAE occurred in the study but was unrelated to study drug.

There were no AEs leading to discontinuation.

There were two patients who discontinued for "subject's choice." These were cases of loss of vascular access and unwillingness to have additional access.

During the study, all patients were hospitalized and monitored. Dr. Muniz concludes, "No patient had severe AEs... In general, safety assessments, including clinical laboratory evaluations, did not reveal any unusual safety results of concern for this medication class."

5. Study OC96-0602, Open-Label Single-Dose Safety Data, n=13

Study OC96-0602 was a small OL PK and safety study in patients 5-12 years who were hospitalized and receiving opiates other than oxycodone, and who were expected to continue to need opiates for at least 4 days. The study was a randomized crossover design comparing plasma oxycodone concentrations in children after either a single dose of OxyContin or a

single dose of IR oxycodone. The PK results of this early study were used in the power calculation for Studies OXP1005 and OXP3003. The study was conducted between 1997 and 1998. The final study report is dated May 16, 2001.

The planned enrollment was 24 subjects, in order to have 20 completers. Only 13 patients actually enrolled, leading to 11 completers. Data from these 11 completers was deemed sufficient for PK purposes. The enrolled patients ranged from 6-12 years.

Two patients discontinued after completing only the first period. The events leading to discontinuation were moderate pruritus and inability to obtain IV access.

Dr. Muniz states, "The most common adverse event was fever (IR oxycodone, 25%; OxyContin, 33%), which was expected in a postoperative population and was not regarded as drug-related. All other adverse events occurred in 1 or 2 subjects each. Adverse events judged to be drug-related were pruritus, nausea, and vomiting. There was no apparent difference between IR oxycodone and OxyContin® in the incidence or type of adverse events. There were no deaths or serious adverse events. In summary, there were no unexpected safety concerns in either the IR oxycodone or OxyContin formulation."

6. Study OXP3004, Open-Label Safety Data, n=10

From Dr. Muniz's review, "The purpose of this study, conducted between March 2003 and February 2004, was to evaluate the safety of the conversion from immediate-release oxycodone (OxyIR) to controlled-release oxycodone (the original OxyContin formulation) in children aged 6 to ≤ 16 years. PK modeling performed on the results obtained from Study OC96-0602 (discussed above) indicated that the 1:1 conversion ratio from OxyIR to OxyContin recommended for adults in the approved OxyContin tablets package insert was also appropriate for children. This study evaluated the safety of the 1:1 conversion ratio by measuring respiratory rate, hemoglobin oxygen saturation, and somnolence in the pediatric population."

The study was discontinued early when the Sponsor ceased the pediatric development program in 2004. At that time, only 10 of the planned 100 patients had been enrolled. Seven of the 10 completed the study.

Two SAEs occurred during the study and were not considered related to study drug.

Two patients discontinued due to AEs. One patient discontinued while taking IR oxycodone and prior to the conversion to OxyContin. That patient discontinued because of vomiting. One patient discontinued during treatment with OxyContin for bone pain/disease progression.

Dr. Muniz concluded that there were no unanticipated safety findings in this study.

**7. Study OTR3002, Open-Label Continuation Study, n=23
Six – Sixteen Years, OxyContin**

This was an OL continuation study for patients who completed four weeks of treatment with OxyContin in Study OTR3001. Patients could be treated for up to six months in this study. Twenty-three patients enrolled in the study. There were nine patients 6-12 years and 14 patients 12-16 years.

The median duration of exposure was 198 days and the median daily dose of OxyContin in the study was 25 mg.

Discontinuations due to AEs
There were no AEs leading to treatment discontinuation. There were four SAEs that were not considered related to study drug.

From Dr. Muniz's review, "The most common TEAEs during OTR3002 occurred in the SOCs of gastrointestinal disorders (including vomiting, 4 patients, 17.4%), and general disorders and administration site conditions (including pyrexia, 5 patients, 21.7%). Most of these events were considered by the investigator to be mild or moderate in intensity; 3 patients (13.0%) experienced severe TEAEs during the extension study, and 1 of these 3 patients (4.3%) experienced a TEAE of fatigue that was considered by the investigator to be severe and related to treatment."

AEs of Special Interest, Somnolence

In Studies OXP1005 and OXP3003, somnolence was rated after patients received IR oxycodone for acute pain. The University of Michigan Sedation Scale (UMSS) was used to assess somnolence. The UMSS is a 5-point scale as follows: 0 = awake/alert, 1 = sleepy/responds appropriately, 2 = somnolent/arouses to light stimuli, 3 = deep sleep/arouses to deeper physical stimuli, and 4 = unarousable to stimuli.

Dr. Muniz presents the results of this evaluation. For Study OXP1005, he states, "In summary, mean somnolence scores for all patients across all dosing intervals remained low and were similar among the 3 pediatric age groups: at 1h postdose evaluations (including 0 to < 6h) ranged from 1.0 to 1.2 (sleepy/responds appropriately), and at 6 h postdose evaluations (including 0 to < 6 h) ranged from 0.9 to 1.0." Given the oxygen saturation findings in the 1-6 month age group in Study OXP1005, it seems somewhat surprising that the somnolence data was similar among the 3 pediatric age groups.

For Study OXP3003, Dr. Muniz states, "In summary, the mean somnolence scores for the 1 hour and 6 hour post-dose evaluations overall were low (less than 1), with no significant difference between dose groups."

Across both studies, there were several patients who were rated deeply sedated (score of 3) and, in Study OXP3003, one patient was rated unarousable (score of 4).

In Study OTR3001, Dr. Muniz states, "There were no patients with treatment-emergent clinically significant somnolence events. There was 1 (3.7%) patient in the younger cohort and there were 2 (1.6%) patients in the older cohort with somnolence scores 3 (deeply sedated) at any point during treatment. No patient had a somnolence score of 4 (unarousable) at any point during the study."

Dose Dependency for Adverse Events

In section 7.5.1 of his review, Dr. Muniz discusses dose-related AEs. He correctly points out that the only controlled data available to address dose-dependency comes from Study OXP3003, the study of IR oxycodone in patients 6-16 years. In that study, pyrexia and constipation appear to be dose-related. The use of concomitant opioids for rescue medication may obscure any analysis of dose dependency.

As discussed above for Study OXP1005, there were different dosing cohorts for the patients older than one month. However, patients were not randomized to these groups, making any statements about dose dependency difficult.

Time Dependency

In his review, Dr. Muniz provides a comparison of the AE profile of the patients enrolled in Study OTR3001 and the AE profile experienced by the subgroup of those patients once they were enrolled in Study OTR3002. Based on that comparison, there is not a suggestion of time dependency for any of the AEs observed. Dr. Muniz also comments on the limitations of this approach.

Postmarket Experience

The Sponsor provided a review of their postmarketing data for OxyContin over the lifecycle of the product, spanning the years 1995-2014. They report 2,411 pediatric cases, 2,320 of them from the United States. About 1,400 of the reports are spontaneous reports, while about 930 are from the RADARS (Researched Abuse, Diversion, and Addiction-Related Surveillance) system. Dr. Muniz describes the RADARS database as follows: "The RADARS system was designed by Purdue in 2002 to track and analyze patterns of opioid drug abuse, not to track individual cases. RADARS operations were transferred from the Sponsor to Rocky Mountain Poison and Drug Center (RMPDC) in 2006. Since that transfer, Purdue no longer receives or has access to individual cases from the Poison Control Center's Study, or from any other component of the System."

The majority of events in patients 13-17 years are related to abuse, dependence, and overdose. The majority of events in patients less than 13 years are related to accidental exposure. After his review of the Sponsor's report, Dr. Muniz raises two issues. First, the term "medication errors" is used for about 5% of the reports in the 651 cases 1-12 years. Because this is a term often used to describe errors preventable through clearer labeling, clarification of the term as it is used in these cases is needed. Second, he states, "Although a large number of AEs reported within the Psychiatric disorders SOC are related to substance abuse and misuse, when taken as

a whole mood disturbances and related suicidal and parasuicidal behaviors are not insignificant, particularly in an adolescent population that is statistically at risk for such psychiatric problems. Therefore, I recommend that some language describing these should be added to the label."

Discussion

Dr. Muniz concludes that the safety data for OxyContin and IR oxycodone submitted in this supplement are consistent with the known safety profiles of OxyContin and oxycodone in adults. He believes labeling for the safe use of OxyContin in opioid-tolerant patients, 11 years and older, is supported by this supplement. He notes that data are available for only 14 patients treated with OxyContin less than age 11 years. I agree with his assessment. Labeling will characterize the safety findings described above.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not deemed necessary for this application.

10. Pediatrics

As already mentioned, the NDA for reformulated OxyContin, NDA 22272, did not trigger PREA because reformulated OxyContin was approved while the original formulation was still marketed (and reformulated OxyContin is not considered a new dosage form).

Pediatric Exclusivity
On May 5, 2015, this supplement was discussed at the Pediatric Exclusivity Board. A separate memorandum summarizing the final determination is currently being prepared. The following (b) (4) were discussed at the meeting.

(b) (4)

Pediatric Review Committee (PeRC)
This supplement was also discussed with PeRC on May 13, 2015. In addition to the issues discussed with the Pediatric Exclusivity Board, (b) (4) One possibility discussed was (b) (5)

11. Other Relevant Regulatory Issues

DSI Inspections
The Clinical Inspection Summary was prepared by John Lee, MD with concurrence from Janice Pohlman, MD, MPH and Kassa Ayalew, MD, MPH.

Inspections were performed at two sites in Study OTR3001. Additionally, the site of Dr. Hammer at Stanford was inspected for both Studies OXP1005 and OXP3003. The sites were selected for inspection based primarily on the larger numbers of patients enrolled compared to other sites.

Name	Number Randomized	Final Classification
Peter Szmuk, MD University of Texas-Southwestern	Study OTR3001 Site 1863A: 15 patients	Preliminary VAI
Andrea Orsey, MD Connecticut Children's Medical Center	Study OTR3001 Site 1360A: 17 patients	Preliminary VAI
Gregory Hammer, MD Stanford Medical Center	Study OXP1005 Site 33A: 26 subjects	Preliminary VAI
Gregory Hammer, MD Stanford Medical Center	Study OXP3003 Site 33A: 26 subjects	

Key to Classifications
NAI = No deviation from regulations
VAI = Voluntary action indicated (minor GCP violations)
OAI = Significant deviations from regulations; data unreliable

A Form 483 was issued at Site 1863A due to a limited number of deficiencies that were considered minor, isolated, and unlikely to be significant by Dr. Lee. Overall, the data from the site appeared to be reliable.

A Form 483 was also issued at Site 1360A due to a limited number of deficiencies that were all considered to reflect poor recordkeeping of otherwise adequate study conduct. Overall, the data from the site appeared to be reliable.

The Form 483 issued for Dr. Hammer's site in Studies OXP1005 and OXP3003 reflected a limited number of deficiencies that were considered minor, isolated, and unlikely to be significant by Dr. Lee. Many appeared to be related to poor recordkeeping of otherwise adequate study conduct. Overall, the data from the site appeared to be reliable.

One comment from the Form FDA 483 deserves mention. The form states, "The temperature log for the freezer did not include temperature records for the first nine of the total 15 months of PK blood sample storage." Dr. Lee commented, "The inadequate freezer temperature log may indicate more than inadequate recordkeeping and may include inadequate PK blood sample handling and storage for much of the study period (nine of 15 months). A comparison of the PK data from this CI site with those from other CI sites may be helpful in evaluating the reliability of the PK data from this CI site." This is discussed in Section 5 Clinical Pharmacology of this review.

Dr. Lee concludes his Clinical Inspection Summary:

> "For all four study-sites audited, the observed GCP deficiencies consisted of those cited on Form FDA 483 and additional uncited discussion items. Whether cited or verbally discussed, most were minor, and all were isolated and/or otherwise unlikely to be significant. Study conduct appeared adequate at all three CI sites inspected, as did IRB oversight and sponsor monitoring of CI's study conduct. All audited study data were verifiable among source records, CRFs, and NDA data listings. The data from the four audited study-sites appear reliable as reported in the NDA.
>
> Note: For all three CI sites inspected, the establishment inspection report (EIR) has not been received from the field office and the final inspection outcome remains pending. Upon receipt and review of each EIR, an addendum to this clinical inspection summary (CIS) will be forwarded to the review division if the final inspection outcome differs from the preliminary outcome reported in this CIS. Otherwise, OSI's inspection close-out correspondence with each CI copied to the review division will indicate EIR review completion without new significant findings."

Financial Disclosures

According to Dr. Muniz's clinical review, the Sponsor has not identified any financial arrangements that would affect the approvability of this application.

REMS

OxyContin is part of the ER/LA Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS), which requires companies to make available to health care professionals educational programs on how to safely prescribe ER/LA opioid analgesics and to provide Medication Guides and patient counseling documents containing information on the safe use, storage, and disposal of ER/LA opioids. Modifications to the REMS may be needed at the time of approval of this supplement based on the final labeling.

12. Labeling

The Sponsor has stated that [redacted] (b) (4)

For OxyContin, the Sponsor has submitted proposed labeling in the pediatric supplement. The Sponsor proposes to extend the current indication to [redacted] (b) (4). Specifically, the Sponsor proposes to modify the current statement in Section 8.4 Pediatric Use to say, [redacted] (b) (4) ."

Notably, the current labeled indication does not distinguish between the treatment of opioid-naïve adults and opioid-tolerant adults and dosing instructions are provided for both groups of patients. The Sponsor [redacted] (b) (4)

The review team has prepared draft labeling with different proposals than those of the Sponsor. This labeling will be sent to the Sponsor and will be the subject of further discussions. The review team believes labeling should only support use in opioid-tolerant pediatric patients 11years of age and older who are already on and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally, or its equivalents.

Labeling should include the conversion table that was studied in Study 3.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

OxyContin: At this time, I do not recommend Approval of OxyContin for the treatment of pediatric patients ages 6-10 years. I do not believe the limited experience with OxyContin in Study OTR3001, with 15 patients 6-10 years, is enough to adequately characterize the age-specific safety profile in that subgroup. A greater number of patients was treated in the 11-16 year age group, n=140. I consider this a sufficient safety experience to support approval. For the chronic pain indication, the current approach is to allow efficacy in adults to be extrapolated to pediatric patients 7 years and older if exposure similar to adults can be achieved in the pediatric patients. The Sponsor has demonstrated through their population-PK analysis that similar exposure can be achieved in patients 11-16 years. Therefore, efficacy, as well as safety, in this age group is supported by data included in this supplement.

The 11-16 year age group is one particularly susceptible to misuse, abuse, addiction, and overdose as evidenced by the postmarketing data provided by the Sponsor. Continued vigilance for these events is warranted.

IR Oxycodone Oral Solution: The Sponsor states (b) (4) Nevertheless, the following can be said about the data submitted from Studies 1 and 2.

For the acute pain indication, the current approach is to allow efficacy in adults to be extrapolated to pediatric patients 2 years and older if exposure similar to adults can be achieved in the pediatric patients. Efficacy studies are required for birth to < 2 years. The Sponsor has demonstrated through their population-PK analysis that similar exposures to adults can be achieved in patients ≥ 2 years with their oxycodone oral solution. Therefore, efficacy for acute pain in this age group has been supported. The Sponsor has additionally provided results from a randomized, controlled trial to support the efficacy of their oxycodone liquid for the treatment of acute pain. While Study OXP3003 was not optimally designed, having no stated primary outcome measure and no stated primary analysis plan, the results observed in the study are not contrary to the efficacy extrapolated from the adult experience. Also, I believe the Sponsor has provided adequate data to support the safety of oxycodone oral solution in pediatric patients ≥ 2 years.

An adequately-controlled efficacy study for acute pain from birth to < 2 years has not been performed with the Sponsor's oral solution, so efficacy is not established for this age group. There is an outstanding information request to the Sponsor to provide narratives for several patients enrolled in Study OXP1005.

(b) (5)

Risk Benefit Assessment

The 11-16 year age group is one particularly susceptible to misuse, abuse, addiction, and overdose. Continued vigilance for these events is warranted.

OxyContin provides the convenience of every-12-hour dosing versus the every-4-6-hour dosing needed with available IR oxycodone products. In addition, the longer dosing interval may reduce the need to interrupt sleep for repeated dosing in some patients with chronic pain.

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/s/

JOHN J FEENEY
05/26/2015